The genetic basis of intradural spinal tumors and its impact on clinical treatment

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Genetic alterations in the cells of intradural spinal tumors can have a significant impact on the treatment options, counseling, and prognosis for patients. Although surgery is the primary therapy for most intradural tumors, radiochemotherapeutic modalities and targeted interventions play an ever-evolving role in treating aggressive cancers and in addressing cancer recurrence in long-term survivors. Recent studies have helped delineate specific genetic and molecular differences between intradural spinal tumors and their intracranial counterparts and have also identified significant variation in therapeutic effects on these tumors. This review discusses the genetic and molecular alterations in the most common intradural spinal tumors in both adult and pediatric patients, including nerve sheath tumors (that is, neurofibroma and schwannoma), meningioma, ependymoma, astrocytoma (that is, low-grade glioma, anaplastic astrocytoma, and glioblastoma), hemangioblastoma, and medulloblastoma. It also examines the genetics of metastatic tumors to the spinal cord, arising either from the CNS or from systemic sources. Importantly, the impact of this knowledge on therapeutic options and its application to clinical practice are discussed.

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INTRADURAL spinal tumors have an incidence of 0.64 per 100,000 person-years and account for 3% of primary CNS tumors.⁷⁸ Although intradural spinal tumors represent a limited overall tumor burden in the population, these tumors frequently cause significant morbidity associated with long-term survival. This review will focus on the known genetic and molecular underpinnings of intradural spinal tumors and on the potential clinical impact of this knowledge (Table 1).

Genetic alterations provide information about a tumor's pathophysiological origin and may also serve as markers for evaluating clinical outcomes. Accordingly, knowledge about the mutations in an individual's tumor can more precisely define a patient's prognosis and risk for cancer recurrence, which may meaningfully inform counseling.⁵¹ Variation in genetic alterations may also inform tumor classification and identify cells of origin for different tumor

types, as has been shown for medulloblastoma.³⁰ Outcome studies based on genetics may prompt reconsideration of standard therapies for broad tumor categories, as clinical evidence may suggest tailored chemoradiation therapies. Enticingly, a deeper genetic understanding provides the opportunity to investigate targeted therapies, particularly to combat aggressive tumors and recurrence in long-term survivors. The most recent development of a targeted inhibitor has been the PD-1 inhibitor nivolumab to treat patients with melanoma.⁸⁸ Although improved knowledge about the molecular workings of tumors is unlikely to challenge the primacy of surgical treatment in the immediate future, a better understanding of tumor genetics may lead to better treatment for intradural spinal tumors.

Intradural tumors are classified as extramedullary or intramedullary, depending on their relationship with the spinal cord. Each of these 2 types is associated with a cer-

ABBREVIATIONS ALK = anaplastic lymphoma kinase; BRAF = B-Raf proto-oncogene, serine/threonine kinase; EGFR = epidermal growth factor receptor; GBM = glioblastoma; HIF1 α = hypoxia-inducible factor 1 α ; ISCM = intramedullary spinal cord metastasis; MAPK = mitogen-activated protein kinase; MMP-9 = matrix metalloproteinase 9; mTOR = mechanistic target of rapamycin; NF = neurofibromin; NST = nerve sheath tumor; p53 = the protein p53; PDGF = platelet-derived growth factor; PI3K = phosphoinositide 3-kinase; PKB = protein kinase B; PTEN = phosphatase and tensin homolog; SHH = sonic hedgehog; SMARCE1 = SWI/SNF-related matrix-associated actin-dependent regulator of chromatin E1; VEGF = vascular endothelial growth factor; VHL = von Hippel-Lindau.

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TABLE 1. Summary literature overview of spinal cord tumors, their incidence, and the genes implicated in their formation and development

	Authors & Year	Spinal Cord Tumor	Incidence (%)		Genes & Chromosomal Changes
			Children	Adults	
Arsilantas et al., 2003; Sayagues et al., 2006; Barresi et al., 2011; Barresi et al., 2012; Smith et al., 2013; Smith et al., 2014		Meningioma	7	38	<i>NF2</i> , <i>MMP-9</i> , & <i>SMARCE1</i> ; loss of chromosome 1p, 9p, 10q, or 22 or gain of 5p or 17q
Ebert et al., 1999; Singh et al., 2002; Johnson et al., 2010; Bettgowda et al., 2013		Ependymoma	22	21	<i>NF2</i> , homeobox B5 (<i>HOXB5</i>), phospholipase A2 group 5 (<i>PLA2G5</i>), & inter- α -trypsin inhibitor heavy chain 2 (<i>ITIH2</i>); loss of chromosome 10q or 22q or gain of chromosome 18
Dow et al., 2005; Hulsebos et al., 2007; Jett & Friedman, 2010; Kim et al., 2014; Schroeder et al., 2014		NST (neurofibromas, schwannomas)	14	23	<i>NF1</i> , <i>NF2</i> , large tumor suppressor kinase (<i>LATS1</i>), & SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B (<i>SMARCB1</i>)
Horbinski et al., 2010; Govindan et al., 2011; Hawkins et al., 2011; Wu et al., 2012 ¹²¹		Astrocytoma	32, 11 (pilocytic)	0.8 (pilocytic) (glioblastoma)	<i>PTEN</i> , p16, <i>BRAF</i> (<i>BRAF</i> KIAA1549 & V600E mutations), p53, & replication-independent histone 3 variant H3.3 (<i>H3F3A</i>) (Lys27Met & Gly34Arg mutations); 9p21del & 10q23del
Prowse et al., 1997; Frantzen et al., 2000; Gläsker, 2005; Takai et al., 2010; Haddad et al., 2013		Hemangioblastoma	Rare	3	<i>VHL</i>
Mumert et al., 2012; Wu et al., 2012; ¹²² Phi et al., 2013; Jenkins et al., 2014		Disseminated medulloblastoma	18–46	Rare	<i>SHH</i> , <i>Eras</i> , <i>Lhx1</i> , <i>Ccrk</i> , <i>Akt</i> , <i>Armt</i> , & <i>Gdi2</i> , inhibitor of differentiation 3 (<i>ID3</i>), p53, & Patched 1 (<i>PTCH1</i>)
Nelson et al., 1995; Ree et al., 1999; Miller et al., 2003; Roodman, 2004; Albiges et al., 2005; Bartels et al., 2008; Sciubba et al., 2010; Gainor et al., 2013; Sutcliffe et al., 2013		Disseminated metastatic cancer	Rare	6, spinal cancer	<i>ALK</i> , <i>BRCA1</i> , <i>Her2/Neu</i> , & nuclear protein transcriptional regulator 1 (<i>NUPR1</i>)

tain pathological development and requires distinct clinical treatment approaches (Fig. 1). Intramedullary tumors account for 5%–10% of all spinal tumors but are more common in children.¹¹² Among patients 19 years of age or younger, ependymomas (22%), nerve sheath tumors (NSTs; 14%), pilocytic astrocytomas (11%), and meningiomas (6%) are the most common intradural tumors,⁷⁸ whereas in patients older than 20 years of age, meningiomas (38%), NSTs (23%), and ependymomas (21%) are the most common (Fig. 2). Less frequent diagnoses of intradural tumors in adults include lymphomas (2%), glioblastomas (GBMs; 3%), hemangiomas (3%), and pilocytic astrocytomas (0.8%). Systemic metastatic disease may also spread within the spinal dura or cord but is most commonly limited to the extradural space. Although many other intradural lesions, such as vascular malformations (for example, cavernous angiomas and arteriovenous malformations), cysts, lipomas, dermoids/epidermoids, and paragangliomas, should be considered, the genetics of these specific pathologies are not included in this review.

Nerve Sheath Tumors

Although both neurofibromas and schwannomas arise from Schwann cells, each of these tumor types displays distinct clinicopathological characteristics during the formation of intradural, extramedullary spinal tumors. Spinal NSTs account for 23% of intradural spinal tumors in adults and for 14% in pediatric patients.¹⁸ Most spinal NSTs (75%–80%) reside intradurally, but about 10%–15% of these tumors extend through the dural root sleeve as a dumbbell-shaped tumor with intradural and extradural components; 10% of spinal NSTs are located extramedullary and 1% are located intramedullary.⁶⁷ Furthermore, 0.7% of spinal NSTs are malignant, resulting in an exceedingly poor prognosis (that is, a median overall survival of 22 months), irrespective of cranial or spinal location.⁸⁷

Malignant NSTs may arise without known preexisting lesions in both cranial and spinal cases, suggesting that tumor malignancy may develop without obvious transformation of a low-grade tumor.

Nerve sheath tumors, as well as other intradural spinal cancers, are more common in patients with neurofibromatosis Type 1, a condition that results from a mutation in the neurofibromin 1 (*NF1*) gene located on chromosome 17q11.⁴⁸ *NF1* encodes a protease involved in Ras-GTP phosphorylation, which reduces activation of downstream mitogen-activated protein kinases (MAPKs) involved in cell proliferation and survival. Mutations in *NF1* show an incidence of 1 in 3000 people and are associated with neurofibroma formation in the spine and in peripheral nerves. In addition, *NF1* mutations are associated with an elevated risk for the development of malignant peripheral NSTs and of a set of diverse tumors, including optic nerve gliomas, rhabdomyosarcomas, pheochromocytomas, and carcinoid tumors. Although familial *NF1* is transmitted in an autosomal dominant manner, sporadic mutations of *NF1* are observed in 50% of cases of spinal neurofibromas, with missense and nonsense mutations being the most common types.

Mutations in the neurofibromin 2 (*NF2*) gene, located on chromosome 22q12.2, also play a role in NSTs of the spine. Familial neurofibromatosis Type 2 most commonly arises as a germline mutation in *NF2*, also known as *merlin*, and has a prevalence of 1 in 33,000.²³ The NF2 protein is member of the ERM (ezrin, radixin, and moesin) family of proteins, linking cytoskeletal components with proteins of the cell membrane that regulate cytoskeletal dynamics and cell-to-cell communication. Mutations in *NF2* may lead to the development of vestibular schwannomas (classically bilateral tumors of cranial nerve VIII), neurofibromas, ependymomas, gliomas, and meningiomas.^{19,97} Approximately two-thirds of patients with neurofibromatosis Type 2 develop spinal tumors, which include spinal epen-

FIG. 1. Illustration showing the distribution of the most common primary spinal cord tumors by type and location. Copyright Fotosearch (www.fotosearch.com). Published with permission.

FIG. 2. Pie charts showing the distribution of primary spinal cord lesions in (left) pediatric (age 0–19 years) and (right) adult (age 20 years or older) patients; the charts were produced with data from the Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report. Data were aggregated from the National Program of Cancer Registries and Surveillance, Epidemiology, and End Results databases from 2007 to 2011, including only primary cancers. *All or some of this histological type are included in the CBTRUS definition of gliomas, including ICD-O-3 histological codes 9380–9384, 9391–9460, and 9480. Percentages may not add up to 100% because of rounding. ^aIncludes embryonal tumors, other tumors of cranial and spinal nerves, other hematopoietic neoplasms, germ cell tumors, neoplasms unspecified, and all other. ^bIncludes oligodendroglioma, anaplastic oligodendroglioma, oligoastrocytic tumors, glioma malignant, choroid plexus tumors, not otherwise specified, other neuroepithelial tumors, and neuronal and mixed neuronal-glial tumors. ^cIncludes diffuse astrocytoma, anaplastic astrocytoma, and unique astrocytoma variants. From Ostrom et al., *Neuro-Oncology* 16:iv1–iv63, 2014. Copyright Oxford University Press. Published with permission.

dymomas, meningiomas, and NSTs. Mutations of *NF2* in spinal ependymoma and meningioma are reviewed below.

One study reported a mutation in the gene for large tumor suppressor kinase (*LATS1*), a downstream mediator of *NF2*, in a case of spinal schwannoma in a patient with Li-Fraumeni syndrome and with a germline mutation in the gene for the protein p53, but the clinical relevance of these alterations remains unknown.⁵⁷ Mutations in *INI1/SMARBI*, a gene involved in chromatin remodeling, have been observed in familial schwannomatosis similar to mutations in *SWI/SNF*-related matrix-associated actin-dependent regulator of chromatin E1 (*SMARCE1*) in cases of multiple familial spinal meningiomas.⁴³ These results support the importance of these genetic alterations in NSTs of the intradural spinal space but leave open questions about the interaction of *NF2* with associated genetic changes and the potential for targeted therapy.

Treatments for both benign and malignant peripheral NSTs have been initiated, which may open windows into the treatment of spinal NSTs. Recent trials have sought to design treatments that target tumors arising from *NF1* or *NF2* mutations.¹²⁵ Treatment with tipifarnib, a farnesyl transferase inhibitor that reduces upregulated Ras signaling resulting from some *NF1* mutations, was evaluated in a Phase I trial involving children with solid tumors and plexiform neurofibromas, who showed stable disease during the follow-up period of this trial.¹¹⁸ In other trials, however, tipifarnib did not prolong time to imaging-confirmed enlargement of plexiform neurofibromas.¹¹⁷ Other potential targets have been studied in patients with *NF1* mutations and with progressive peripheral neurofibroma during trials of sirolimus (an inhibitor of mechanistic target of rapamycin [mTOR]),¹¹⁶ PD0325901 (an inhibitor of MEK,

a MAPK kinase),⁴⁷ pegylated interferon- α -2b,⁴⁵ imatinib (a c-kit and platelet-derived growth factor receptor- β [PDGFR β] inhibitor),⁸⁹ and sorafenib (inhibitor of c-kit, PDGFR β , RAF, and vascular endothelial growth factor [VEGF] receptor 2);⁵⁵ however, the results of these trials have indicated only limited clinical improvement or were obtained in trials with sample sizes too low to support clinical use of these agents. Such targeted treatment approaches have not yet been attempted in intradural spinal NSTs.

Meningiomas

Meningiomas are extramedullary, intradural tumors arising from meningeothelial arachnoid cap cells within the spinal dura. Spinal meningiomas are the most common spinal tumors in adults, accounting for up to 38% of intradural spinal tumors but only for 6.5% of overall craniospinal tumors in this age group.⁷⁸ Similar histological subtypes are observed in both intracranial and spinal meningiomas, including meningeothelial, metaplastic, psammomatous, transitional, atypical, and clear cell types. The psammomatous, meningeothelial, and transitional subtypes are the most common meningiomas of the spine and, for reasons that are unknown, show a lower risk for recurrence than their intracranial counterparts.^{94,96,101} Compared with resection of other meningioma subtypes, resection of psammomatous spinal meningiomas is associated with poorer neurological outcomes postoperatively.⁹⁶ Although malignant transformation of spinal meningiomas, like that of their intracranial counterparts, does occur, this transformation accounts for just 3% of cases.¹⁰¹

Multiple genes have been associated with spinal menin-

giomas. Several studies have reported deletion of chromosome 22q and of its associated gene *NF2* in cases of spinal meningioma.^{4,95} A comparative DNA microarray study of 7 spinal and 11 intracranial meningiomas found that spinal meningiomas were more commonly associated with the psammomatous and transitional subtypes along with a greater likelihood of chromosome 22 deletion.⁹⁵ In that study, interphase-fluorescence in situ hybridization was used to generate tumor karyotypes, which visualize the cell's entire chromosome set; the results showed that spinal meningiomas were more likely to arise from a single-cell clone rather than from a collection of cells. The study also reported differential expression of 1555 genes in spinal and intracranial meningiomas. Thirty-five of these genes were more highly expressed in spinal meningiomas than in intracranial tumors, including those involved in transcription (that is, *Hox* genes, the *NR4* family of genes, *KLF4*, *FOSL2*, and *TCF8*) and in intracellular (*RGS16*, *DUSP5*, *DUSP1*, *SOC3*, and *CMKOR*) and extracellular (*L6*, *TGFB114*, *IL1B*, *CYR61*, and *CDH2*) signaling.

Another study of 16 patients with spinal meningioma showed that the cells of these tumors most commonly displayed complete or partial loss of chromosome 22, along with loss of 1p, 9p, and 10q and with gain of 5p and 17q, compared with the chromosome complement in the patients' own lymphocytes.⁴ These chromosomal changes were most common in the atypical and anaplastic subtypes. Current clinical treatment algorithms do not distinguish between spinal and cranial meningiomas despite their underlying differences. Furthermore, the above findings suggest distinct genetic mechanisms for these 2 diseases, which may influence the clinical prognosis of the patients affected.

In addition to chromosomal alterations, changes to individual genes have also been observed in spinal meningioma. One study reported that spinal meningiomas had upregulated expression of the matrix metalloproteinase family of proteins involved in cell growth and invasion.⁵ The authors measured gene expression in 58 spinal meningiomas, and upregulated expression of matrix metalloproteinase 9 (MMP-9) was observed in 46% of them. Only 1 case of recurrent meningioma was included, and no overall correlation with survival was detected. In contrast to MMP-9 expression in spinal meningiomas, MMP-9 expression in intracranial meningiomas correlates with a more aggressive histological grade and proliferation index of the tumor and with a poorer prognosis.⁶

Mutations in *SMARCE1*, which is involved in the regulation of secondary DNA structure within chromosomes, have also been reported to be important in the formation of multiple spinal meningiomas.¹⁰⁵ The study by Smith and colleagues identified *SMARCE1* mutations in a group of individuals with familial multiple spinal meningiomas without *NF2* mutations. Furthermore, *SMARCE1* is mutated in cranial meningioma and associated with the clear cell subtype, which is a WHO Grade II tumor that tends to metastasize more frequently than other subtypes.¹⁰⁶ Importantly, many of the extensively studied gene mutations in intracranial meningioma (for example, in the genes differentially expressed in adenocarcinoma of the lung [*DALI*], tissue inhibitor of metalloproteinases 1 [*TIMP1*], *p16*, *p15*, *p14ARF*, *N-Myc* downstream-regulated gene 2 [*NDRG2*],

adaptor-related protein complex 1, $\beta 1$ subunit [*ADTBI*], deleted in liver cancer 1 [*DLC1*], *c-myc*, *bcl-2*, and signal transducer and activator of transcription 3 [*STAT3*]) and their respective molecular pathways have yet to be fully evaluated in spinal meningiomas.⁷⁹ Accordingly, the prognostic impact and the potential for targeted therapy of these genetic alterations still await full elucidation in spinal meningiomas. Current treatments of more aggressive spinal meningiomas are limited, and better identification of critical gene targets may improve therapeutic targeting.

Although the genetic alterations in spinal meningiomas may differ from those in intracranial meningiomas, recent studies have investigated the use of gene targeting and molecular therapies to address both diseases. Oncolytic therapy has used herpes simplex virus 1 (HSV-1), adenoviruses, vaccinia virus, and retroviruses for transfecting genes into tumor cells to induce apoptosis in meningiomas.¹⁶ Experimental transfection with *NF2* in an animal meningioma model⁴⁴ and with the Ras pathway inhibitor *Ha-RasNI7* in an in vitro meningioma model¹⁰³ has been successful. In addition, transfection of small interfering RNA (siRNA) constructs to reduce or silence expression of *cathepsin B* and *MMP-9* genes reduces meningioma migration and invasion in vivo.¹¹³ Similarly, siRNA targeting of *uPAR/cathepsin B* and *uPA/uPAR* genes, involved in the urokinase-type plasminogen activator (uPA) system, reduces markers of tumor angiogenesis in meningioma.³⁶ Some genes involved in intracranial meningioma, including *NF2* and *MMP-9*, may be also suitable targets in spinal meningioma but have not yet been targeted in clinical trials.

Several recent trials have evaluated the potential of the anti-VEGF drug bevacizumab in treating intracranial meningioma.^{38,64,73,76,83} One trial with 48 patients having intracranial meningioma who were followed up for a median period of 18 months showed that 29% of these patients had at least a 20% reduction in meningioma volume;⁷⁶ however, this reduction was not sustained over time, and a molecular analysis yielded no correlation of VEGF pathway expression with treatment responses. Identifying the critical gene targets in spinal meningioma will improve the design of clinical treatments. Such efforts may be aided by advances in tissue engineering, which may make it possible to test therapeutics in vitro before any in vivo administration.²⁶

Ependymomas

Ependymomas are the most common spinal cord tumors in pediatric patients (22%) and are also common in adults (21%).⁷⁸ Most ependymomas in pediatric patients occur intracranially; within the spine, they occur most commonly in the filum terminale or conus.¹¹⁴ In adults, ependymomas most often occur in the cervical spine and filum terminale. Ependymomas are classified as subependymoma or myxopapillary (WHO Grade I), ependymoma (WHO Grade II), or anaplastic (WHO Grade III). In both children and adults, the myxopapillary variant is most prevalent. Although they were previously presumed to originate from ependymal cells in the central canal, both spinal and intracranial ependymomas are now thought to arise from radial glial stem/progenitor cells.^{49,110} Interest-

ingly, the cell of origin may be associated with the clinically observed pattern of this tumor, as spinal ependymomas may be located intramedullary or extramedullary or may represent a combination of both.

Multiple genetic patterns differentiate spinal ependymomas from intracranial ependymomas. In a transcriptomic study of 39 ependymoma tumors, including 10 spinal ependymomas, unbiased hierarchical clustering, which categorizes tumors according to quantitative mRNA expression levels alone, separated samples into supratentorial, posterior fossa, and posterior fossa spine categories.⁶⁰ Spinal ependymomas showed high levels of homeobox B5 (*HOXB5*), phospholipase A2 group 5 (*PLA2G5*), and inter- α -trypsin inhibitor heavy chain 2 (*ITIH2*) expression and low levels of *NF2* expression. In additional studies, an *NF2* mutation was observed in 30%–40% of spinal ependymomas and was observed only in spinal ependymomas in studies that also included intracranial ependymomas.¹⁰⁴ Similarly, another study of 8 spinal and 8 intracranial ependymomas reported significant losses of chromosome 22, on which *NF2* resides, in spinal ependymoma.⁸ In addition, an unexpected partial loss of chromosome 13 was observed. In addition, loss of chromosome 10q has been reported in a study of a small number of spinal ependymomas.²⁰ The overall mutation rates in spinal ependymomas were quite low in this study, averaging 12.9 mutations per spinal ependymoma and 12.8 mutations per intracranial ependymoma (by comparison, rates of up to 450 mutations per tumor have been observed in lung cancer).¹⁰ These lower mutation rates may improve identification of gene targets in spinal ependymomas to expand therapeutic approaches.

A comparative genomic hybridization analysis with custom DNA probes for tumor karyotyping showed chromosomal morphologies that were distinct for intracranial and spinal ependymomas and chromosomal differences among the different histological subtypes (that is, myxopapillary, classic, and anaplastic).¹¹ Balanced chromosomal translocations were observed in 32% of intracranial ependymomas but in only 3% of spinal ependymomas. Gains across entire chromosomes were common in spinal (64%) and adult cranial (56%) ependymomas. Loss of chromosome 22q was observed in 50% of medullary ependymomas, and other chromosomal changes were common in other types (for example, gain of chromosome 1q in pediatric posterior fossa tumors and anaplastic tumors, mutations on chromosome 10 in myxopapillary subtypes, and loss of 6q in adult posterior fossa tumors).

Johnson and colleagues⁴⁹ recently used a novel approach for delineating relative genetic differences between spinal and intracranial ependymomas. This study compared the genetic profiles in human ependymomas compared with those in mouse tumor models. Gene expression patterns in human cranial ependymomas resembled the patterns in mouse neural stem cells in a p16-mutated background (*Ink4a/Arf*^{-/-}). On the other hand, expression patterns in human spinal ependymomas were similar to those in normal mouse neural stem cells. Although limited to a comparison of human and murine gene expression, the observations in this study suggested that spinal ependymomas reflect an adult genotype, whereas intracranial ependymomas reflect a pediatric genetic program. Spinal

ependymomas showed significant losses of chromosome 22q similar to losses observed in intracranial ependymoma, but spinal ependymomas also showed unique gains of chromosome 18, which were not observed in intracranial tumors. These results also support the idea that distinct molecular approaches to treating these tumors would warrant further investigation.

Although studies have identified various molecular targets in ependymomas, few clinical trials have explored the efficacy of treatments involving these targets.¹¹⁹ Investigation of the PI3K signaling pathway in pediatric ependymomas indicated that upregulation of protein kinase B (PKB or Akt protein kinase) and PI3K correlates with poorer progression-free survival.⁹¹ Although both PKB and PI3K are potential therapeutic targets, their expression was lower in spinal ependymomas, which could potentially limit their usefulness in treatments of these tumors. Upregulated expression of epidermal growth factor receptor (EGFR) in intracranial ependymomas correlates with poor prognosis; this association was further demonstrated by targeted inhibition of EGFR with gefitinib and with AEE788, which reduced tumor proliferation in an in vivo model.^{68,100} These results suggest that inhibition of EGFR may prove beneficial in spinal ependymomas, should it be validated as a tumor driver. Subgroup C supratentorial ependymomas have been successfully targeted with the histone deacetylase inhibitors vorinostat and panobinostat.⁶⁹ Targeting of the Notch-signaling pathway with a γ -secretase inhibitor (MK-0752) was well tolerated and achieved stable disease during a Phase I trial in 1 patient with intracranial ependymoma.²⁷

Targeted therapy for spinal ependymomas is also scarcely described in the literature, although a report of a PDGF-expressing tumor that responded to treatment with imatinib suggests that this medication may have a potential for treating such tumors.²⁴ Treatment options involving viral delivery for ependymomas have been limited, but 1 Phase I trial has demonstrated successful retroviral transfection with the herpes simplex virus in an adolescent patient with intracranial ependymoma.⁶² The results of this trial indicated elevated levels of interleukin 12 and Fas ligand and of peripheral T cells and B cells, as well as enhanced T-cell activation, consistent with upregulation of the immune system. Another trial investigated expression of EphA2, interleukin-13R α 2, survivin, and Wilms tumor protein (WT1) in pediatric ependymomas as a preliminary basis for use of an existing multiprotein, peptide-based glioma vaccine.¹²⁶ The results of the trial suggested variable expression of these tumor-associated antigens in cranial ependymoma and therefore have potential implications for future clinical trials. Further studies of molecular targets in ependymoma tumors and specifically of application in treatments for spinal ependymomas are warranted.

Astrocytomas

Intramedullary spinal astrocytomas arise from astrocytes within the spinal cord. They account for 32% of all spinal cord tumors in children and for 4% of all spinal cord tumors in adults⁷⁸ and comprise approximately 90% of all intramedullary spinal cord tumors in pediatric patients.⁷⁸ Similar to the astrocytic tumors in the brain, astrocytomas

in the spine include pilocytic astrocytoma (WHO Grade I); diffuse, low-grade, or fibrillary astrocytoma (WHO Grade II); anaplastic astrocytoma (WHO Grade III); and GBM (WHO Grade IV).⁷² Pilocytic astrocytomas account for 11% of tumors in the spines of children but are rare in the spines of adults (0.8%). Fibrillary astrocytomas are the most common subtype in adults (89%), and malignant astrocytoma accounts for 10% of intramedullary astrocytomas. Astrocytomas with WHO Grade II and above occur in 20.7% of pediatric and adolescent spinal cord tumors compared with 3.2% of adult spinal cord tumors. Most astrocytomas (60%) occur in the cervicothoracic segments, although these lesions are observed throughout the spine.

Although many studies have investigated the genetics of intracranial astrocytomas, fewer studies have probed the genetics of astrocytomas occurring in the spinal cord. Some common mutations observed in cranial GBMs are also noted in spinal astrocytomas, including mutations in the *p16* gene, the phosphatase and tensin homolog (*PTEN*) gene, the B-Raf proto-oncogene (*BRAF*), *p53*, and the replication-independent histone 3 variant H3.3 gene (*H3F3A*). In 1 study of 9 cases of pilocytic astrocytoma, mutations were found in *p16* and on 9p21, the chromosome where it is located, as well as on the *PTEN*-containing chromosome 10q23.⁴⁰ The *p16* gene encodes a cell-cycle regulatory protein, and its mutation may result in unregulated cell proliferation. *PTEN* is involved in regulating phosphorylation of membrane-bound phosphatidylinositol, which influences downstream PKB/Akt signaling to induce cell proliferation, migration, and mRNA translation. Importantly, numerous downstream targets from *PTEN* have been identified, such as mTOR and Akt, and several chemical antagonists of these effector proteins are currently under clinical investigation for managing cranial astrocytoma, which may offer the possibility of expanding treatments to spinal astrocytoma.⁹³

In 2 studies of spinal astrocytoma, the *BRAF* gene has also been observed to contain mutations, namely the *BRAF-KIAA1549* fusion gene and *BRAF*^{V600E} mutation.^{39,40} *BRAF* is a membrane-bound proto-oncogene involved in regulating cell proliferation and survival. Mutations in the *BRAF* gene result in a constitutively active protein that promotes tumor formation. Constitutive activation of *BRAF* has not been shown to consistently result in a poorer prognosis for patients with cranial and spinal astrocytomas.^{39,42} The *BRAF* protein has been successfully targeted in some cancers, such as in melanoma treatment with vemurafenib, and has been tested as a potential target in cranial GBM.⁴²

High expression of *p53*, which may be observed after a mutation in its gene, has been observed in a few cases of spinal GBMs.³⁴ Although *p53* mutations have been commonly reported and have been extensively studied in cranial GBMs, further investigation is required to study *p53* mutation levels, mutation subtypes, and interaction with other *p53* pathway proteins such as MDM2, an E3 ubiquitin ligase that affects *p53* activity, and the Rb protein, a tumor suppressor, in spinal GBMs.²² Various targets within the *p53* pathway have been identified but have yielded limited efficacy in controlling GBM. In addition, mutations in *H3F3A*, which is involved in regulating DNA

folding and gene expression, have been observed in 36% of nonbrainstem GBMs.¹²¹ Two distinct mutations, Lys-27Met and Gly34Arg, have been predominantly associated with brainstem or spine and supratentorial GBMs, respectively.¹²¹ Unlike for many of the other spinal tumor types, multiple mutational targets have been identified for astrocytoma owing to the development of treatments for cranial astrocytoma. Further investigation into the efficacy of these treatments for recurrent or aggressive astrocytoma of the spine may be warranted.

Several studies have investigated gene targeting and clinical efficacy of various agents in the treatment of intracranial astrocytoma, namely GBM, but few studies have explored potential treatment of spinal astrocytomas.⁵¹ Targeting of the PI3K/PKB/mTOR pathway,^{35,93} *p53*,²² and *BRAF*⁹⁰ has been attempted in intracranial gliomas with limited success; many of these targeted approaches have not yet been tested in astrocytoma of the spinal cord because of the greater rarity of this condition. One potential target for inhibiting spinal cord astrocytoma formation and progression is hyaluronan, a nonsulfated glycosaminoglycan distributed throughout connective and neural tissue. For example, oligomers to hyaluronan suppressed the in vivo growth of spinal cord astrocytoma.⁶⁶ Another potential approach involves treatment with genetically modified *Salmonella typhimurium* to suppress in vivo growth of a spinal astrocytoma model;⁵⁸ however, the mechanism for this approach remains unknown.

Many researchers have studied the feasibility of targeting gliomas with viral delivery methods, which have attracted significant clinical interest.¹⁷ As of 2012, approximately 20 clinical trials with 7 different oncolytic viruses in the treatment of GBM had been completed,¹²⁰ and although the safety of this approach has been evident, its clinical efficacy and application remain under investigation. This potential treatment approach can be applied to spinal astrocytoma, which shares many of the same genetic alterations with its intracranial counterpart.

Hemangioblastomas

Hemangioblastomas are benign tumors that account for 2%–8% of intramedullary tumors and show a low prevalence in childhood.^{28,33,37,78} Approximately 25% of hemangioblastoma patients have evidence of familial von Hippel-Lindau (VHL) disease characterized by the *VHL* mutation. The *VHL* gene encodes an E3 ubiquitin ligase that targets hypoxia-inducible factor 1 α (HIF1 α), which regulates cell metabolism and vascular proliferation. The *VHL* gene resides on chromosome 3p25–26 and is transmitted in an autosomal dominant fashion with 90% gene penetrance. VHL disease results in symptoms at earlier ages, including associated tumors such as CNS hemangioblastoma, retinal angioma, renal cysts, clear cell renal carcinoma, pancreatic cysts, pheochromocytoma, epididymal cystadenoma, and pancreatic neuroendocrine tumor. A CNS hemangioblastoma can occur without (Type I) and with (Type II) pheochromocytoma.

Approximately 80% of hemangioblastomas develop in the posterior fossa, and 20% occur in the cervical or lumbar spine.⁷⁸ Missense mutations are common in familial VHL disease, but sporadic mutations and deletions have

also been observed in sporadic and VHL-related spinal hemangioblastoma. Hypermethylation of *VHL* is also a possible mechanism of protein inactivation.⁸² The impact of *VHL* mutations on spinal hemangioblastoma has not been extensively studied, but 1 study reported that spinal hemangioblastomas were strongly associated with the VHL syndrome (in 88% of cases) but occurred less frequently in sporadic cases (21%) and often were associated with significant VHL expression in multilevel disease.¹⁰⁹ Overall, the understanding of the role of mutated genes other than *VHL* in spinal hemangioblastoma remains limited.

Potential molecular targets of hemangioblastoma, namely the VEGF and HIF1 α proteins, may offer avenues to treat patients with this tumor type or with other tumors that rely on neovascularization. The anti-VEGF agent and angiogenesis inhibitor bevacizumab has been approved by the US Food and Drug Administration for various tumors, including metastatic ovarian, cervical, breast, colorectal and renal cell carcinoma, non-small cell lung carcinoma, and recurrent GBM. Results from clinical trials with GBM patients have indicated that anti-VEGF therapies such as bevacizumab improved progression-free survival and performance status but not overall survival.⁵³ Targeting HIF1 α reduces growth of GBM in vivo and decreases the expression of both VEGF and glucose transporter 1 (GLUT1), which are implicated in neovascularization and tumor metabolism, respectively.³² Treatment with anti-VEGF inhibitors has been investigated during the in vivo treatment of *VHL*-null renal cell carcinoma¹²³ and of *VHL*-associated retinal hemangioblastomas.⁴¹ A recent study showed that variable expression of *VEGF-A*, *VHL*, and *VEGF-C* along with other genes may predict the efficacy of bevacizumab.¹⁵ Other molecular markers or factors are probably also important in regulating the therapeutic efficacy of bevacizumab. Both anti-VEGF and anti-HIF1 α treatments have shown limited efficacy in managing intracranial tumors and have not yet been fully investigated for hemangioblastomas.

Disseminated Medulloblastomas

Medulloblastomas are malignant brain tumors that arise from cerebellar granule precursor cells in the developing cerebellum of children.^{84,85} Transcriptome analysis in large cohorts of medulloblastoma patients has shown that these lesions make up a diverse set of tumors that differ in gene expression profiles, rates of metastasis, and overall patient survival.^{13,59,111} Most notably in children, an increasingly accepted predictor of shortened survival times is the presence of metastasis to the spine.²¹ Metastasis rates appear to vary among the 4 genetic subgroups of medulloblastoma (17.9% in the Wnt subgroup, 19.1% in the sonic hedgehog [SHH] subgroup, 46.5% in Subgroup C, and 29.7% in Subgroup D).⁷⁵ Medulloblastomas appear to metastasize by disseminating via the CSF to the leptomeningeal spaces of the brain and spine.⁸¹ The high rate of spinal metastases has made craniospinal radiation a mainstay of treatment for medulloblastoma, even if no lesions are visible on spinal images. In addition, the significant morbidity rates associated with craniospinal radiation in pediatric patients have motivated the pursuit of alternative, molecular genetics-guided therapeutic strategies.

Recent studies suggest that expression of distinct genes enables tumor cells to proliferate without surface attachment and to seed the leptomeningeal space. The Sleeping Beauty transposon system has been widely used to probe driver mutations in medulloblastoma. Developed in 1997, it helps insert gene fragments into the genome of animal medulloblastoma models without requiring viral vectors.⁷¹ Furthermore, development of a *Patched* model in mice has shown that overactive SHH signaling plays an important role in medulloblastoma initiation and dissemination within the spinal theca.^{46,71} Furthermore, insertional mutation of *Patched* in cerebellar granule precursor cells has helped identify this cell population as the origin of SHH-dependent medulloblastomas.^{98,124} The Sleeping Beauty system helped identify multiple gene candidates implicated in leptomeningeal dissemination, including *Eras*, *Lhx1*, *Ccrk*, *Akt*, *Arnt*, and *Gdi2*.^{46,71} These genes show high expression in aggressive cases of medulloblastoma and are important in cancer development.

In another study, inhibitor of differentiation 3 (*ID3*) expression was reported to be involved in greater leptomeningeal dissemination and worse prognosis in Group 4 tumors.⁸⁰ *Inhibitor of differentiation* genes encode a family of transcription factors that suppress cell differentiation and regulate cell proliferation and migration in various cancers. Genomic analysis of medulloblastoma metastases to the spinal space is constrained by the limited indication for resection or biopsy, only rarely providing sufficient tissue on which to perform genetic analyses. Further development of genetic models will help identify and test therapeutic targets in medulloblastoma.

Although it is unknown how many different genes are required to initiate and maintain metastasis in individual patients, recent findings suggest that even a single gene mutation can promote metastatic transformation in medulloblastoma and seeding of the spinal meninges. Medulloblastoma models with mutations in *Patched* or *p53* show significant leptomeningeal dissemination and aberrant expression of several genes. In a study by Wu et al.,¹²² 225 mutated genes were observed in the metastatic *Patched* medulloblastoma model, and only 60 of these genes were associated with the primary tumor. Similarly, 72 mutated genes were observed in a *p53*-mutation background, and 8 of these mutations were associated with the original primary tumor. These results support the idea that an individual driver mutation can alter extensive oncological signaling networks and possibly induce therapeutic resistance. They also suggest distinct molecular differences between primary and metastatic diseases, supporting the idea that specific treatment paradigms may be necessary during treatment of disseminated medulloblastoma.

Targeting intracranial medulloblastoma has gained significant interest with the further characterization of the aforementioned 4 molecular subtypes. Several clinical trials have investigated the use of the inhibitors of the Smoothened receptor protein, LDE225, vismodegib, and sonidegib, alone or in combination with temozolomide in the clinical treatment of SHH-dependent medulloblastomas.^{54,65} Current approaches are also seeking to overcome resistance to Smoothened-dependent SHH pathway inhibition through the use of downstream effectors of the SHH pathway and via combinatorial treatments with the PI3K/

mTOR inhibitors arsenic or itraconazole.^{2,9,25,56} Inhibition of other medulloblastoma subtypes has been more limited. Targeting of Wnt pathway–dependent medulloblastomas is currently in progress with a Phase I evaluation of olaparib and veliparib.^{54,65} These compounds inhibit tankyrase-1, an activator of the Wnt signaling pathway that acts by poly-ADP ribosylation of AXIN1 and AXIN2, proteins that are involved in the β -catenin destruction complex. Studies of inhibitors of PI3K/mTOR, MAPKs, EGFR, and VEGF are also ongoing or are in early phases. Many of these agents are currently under investigation in recurring medulloblastoma; however, the extent to which these protein inhibitors target spinal medulloblastoma metastases has not been specifically reviewed.

Disseminated Metastatic Cancers

The extradural vertebral column is most frequently involved in bony metastasis, whereas purely intradural disease is uncommon and accounts for less than 6% of all spinal metastatic diseases.^{7,99,108} Up to 70% of cancer patients have spinal metastatic disease at the time of death, with the most common types arising from lung, prostate, and breast cancers.³¹ Intramedullary spinal cord metastasis (ISCM) is rare and is observed in fewer than 1% of all patients with systemic cancer.¹⁴ Lung and breast cancers are the most common primary tumors for ISCMs,¹⁰⁷ although a diverse range of other cancers, including renal cell carcinoma⁵² and pituitary stalk germinomas,¹⁰² has reportedly metastasized to the intramedullary spinal cord. The most common site for metastatic disease is the thoracic spine (70%), followed by the lumbar spine (20%), cervical spine, and sacrum.⁹⁹ Outcomes for patients with ISCMs are among the poorest of all for patients with intramedullary tumors, with a median length of survival of approximately 4 months from the time of diagnosis.¹⁰⁷

Because of the rarity and heterogeneity of intradural metastatic disease and of ISCMs, precise molecular characterization of these tumors is less robust than that of bony metastatic disease.^{108,115} Non–small cell lung cancer frequently metastasizes to the cranial CNS, but its occurrence within the spinal cord remains rare, being encountered in approximately 2% of patients with this disease.⁷⁷ Mutations in the anaplastic lymphoma kinase (*ALK*) gene in non–small cell lung cancer appear to predispose patients to earlier and more aggressive CNS involvement, with 1 recent case series reporting a 4.2% rate of ISCM in *ALK*-positive individuals.²⁹ The *ALK* gene encodes a transmembrane tyrosine kinase that regulates multiple downstream mitogenic pathways and is involved in various tumors, including lymphoma, neuroblastoma, and non–small cell lung cancer.³ Nearly 15% of all instances of ISCM is attributable to breast cancer.⁵⁰ Although much work has been done on the genetic alterations influencing metastasis to the brain, including mutations in *BRCA1*¹ and *Her2/Neu*,⁷⁰ little progress has been made on evaluating the risk factors for ISCM.

To help overcome the clinical research challenges due to the rarity of ISCM, animal models have been developed to identify candidate genes that increase the risk for ISCM development. The nuclear protein transcriptional regula-

tor 1 (NUPR1), also known as candidate of metastasis-1, a chromatin-binding protein involved in histone regulation, generates intramedullary metastatic breast cancer in an experimental rat model;⁸⁶ however, the specific role of NUPR1 in regulating metastatic spinal disease remains controversial, and no further work has investigated its role specifically in ISCM. The genetic changes in intradural spinal metastases probably differ from those of vertebral body, intracranial, or systemic disease, and this difference may be important for treatment design and strategies. Additional comparisons of intradural and extradural metastatic diseases are warranted to better delineate genetic changes and clinical patterns.

Cancer metastasis is a complex multistep process that remains one of the most poorly understood facets of oncology. The process has been described as involving the initial dissemination of cancer cells from a primary tumor followed by a secondary colonization in a new microenvironment.^{12,61} Cancer metastasis to the spinal cord is rare and difficult to study clinically. Important to the understanding of metastasis has been the discovery of cancer stem cells, which are cells that have the potential to self-renew, form additional cells of a cancer mass, and resist treatment. Targeting of these cancer stem cells has been 1 approach in molecular treatment of metastatic cancer.⁶³ Metastatic cancer types may have some similarities, but they likely also harbor significant genetic differences that necessitate unique therapeutic strategies.

Conclusions

Intradural spinal tumors are often histologically similar to the intracranial counterparts with which they share a name, but otherwise are frequently genetically unique. These specific differences in genetic makeup suggest a potentially different pathogenesis that necessitates consideration of specific treatment modalities. Although resection remains a primary treatment option for most intradural spinal tumors, there is an increasing desire and ability to develop targeted chemotherapeutic interventions that can treat aggressive disease or offer options for salvage therapies. The application of the current knowledge gained from studies of cranial tumors will play an important role in the treatment of spinal cord tumors, despite the genetic differences between spinal tumors and their intracranial counterparts. In addition, specific treatments focused on a single molecular target may be useful across tumor types because of similar mechanisms that underlie their pathogenesis. Because of the rarity of intradural spinal tumors, collaborative, multicenter investigations will be required to fully realize the promise of targeted genetics-based therapies.¹²⁷ Continued elucidation of the genetic features of these tumors will aid in the future design of treatment options and in clinical decision making.

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